CRISPR-mediated activation of a promoter or enhancer rescues obesity caused by haploinsufficiency.

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Public Summary:
A wide range of human diseases result from haploinsufficiency, where the function of one of the two gene copies is lost. Here, we targeted the remaining functional copy of a haploinsufficient gene using CRISPR-mediated activation (CRISPRa) in Sim1 and Mc4r heterozygous mouse models to rescue their obesity phenotype. Transgenic-based CRISPRa targeting of the Sim1 promoter or its distant hypothalamic enhancer up-regulated its expression from the endogenous functional allele in a tissue-specific manner, rescuing the obesity phenotype in Sim1 heterozygous mice. To evaluate the therapeutic potential of CRISPRa, we injected CRISPRa-recombinant adeno-associated virus into the hypothalamus, which led to reversal of the obesity phenotype in Sim1 and Mc4r haploinsufficient mice. Our results suggest that endogenous gene up-regulation could be a potential strategy to treat altered gene dosage diseases.

Scientific Abstract:
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